Echo Contrast–Enhanced Transcranial Ultrasound
Frequency of Use, Diagnostic Benefit, and Validity of Results Compared With MRA

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Background and Purpose—The present study was undertaken to determine the frequency of use of the ultrasound contrast agent (UCA) Levovist in routine transcranial ultrasound (TU). Additionally, we evaluated the diagnostic validity of contrast-enhanced TU using 3-dimensional time of flight MR angiography.

Methods—Indication for the UCA was an insufficient evaluation of the intracranial arteries after a combined approach with transcranial color-coded Duplex and transcranial Doppler examination. We prospectively analyzed every patient referred for TU over 6 months. Additionally, over a 3-month period, TU results were compared with 3-dimensional time-of-flight MR angiography.

Results—Indication for use of UCA was met in 61 of 687 patients (8.8%). After UCA application, a diagnostic result was achieved in 75% of cases during transtemporal and in 81% during transforaminal insonation. The sensitivity and specificity of TU in the diagnosis of intracranial stenosis were 83% and 82%, respectively.

Conclusions—Use of UCA was necessary in 8.8% of the patients. A diagnostic benefit was achieved in 75% to 80% of cases. Contrast-enhanced TU demonstrated a high sensitivity and specificity in the diagnosis of intracranial stenosis.

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Key Words: cerebral arteries • contrast media • ultrasonics

Transcranial ultrasound (TU) is a noninvasive, easy-to-repeat diagnostic technique that is being used widely for the evaluation of cerebral hemodynamics. The limitations of this technique are poor insonation conditions resulting from the thickness of the skull, severe obesity, and very low flow velocities.1 During the last decade, ultrasound contrast agents (UCAs) have been developed to overcome this obstacle. One of them, Levovist, consists of galactose microparticles with an average diameter of 3 μm stabilized by palmitic acid.2,3 The surfaces of these granules serve as foci for the adhesion of air microbubbles, which increase the backscattering of the Doppler signal after intravenous application. Many studies have shown that this UCA is safe, increases diagnostic confidence in ≈75% to 80% of cases,1,4,5 and offers the possibility to assess the pial arteries in both the anterior and posterior circulation over a longer distance.6–9 However, not much is known about the application of these contrast media in a routine clinical setting. Furthermore, UCAs may decrease the diagnostic accuracy of TU for intracranial stenosis by increasing the measured intracranial flow velocities and causing “bubble noise.”10,11

We prospectively analyzed every TU examination performed in our neurological ultrasound laboratory over a period of 6 months and assessed (1) the frequency of use of UCA, (2) its diagnostic benefit, and (3) the validity of UCA-enhanced TU for the diagnosis of intracranial stenosis. During the time of the study, Levovist was the only registered UCA available in Germany.

Patients and Methods

A total of 687 patients from the outpatient or inpatient facilities of the Department of Neurology, Christian-Albrechts-University Kiel were examined during this study. The protocol was approved by the ethics committee of the University Kiel. The study consisted of 2 parts.

Part 1

Over a time period of 6 months, each patient referred to the ultrasound laboratory for TU was examined according to the following protocol. First was the examination of the extracranial carotid and vertebral arteries (VAs) with duplex sonography. The second step was the examination of the basal cerebral arteries with TU over their whole detectable length, ie, the middle cerebral artery (MCA) at a depth of 35 to 65 mm, anterior cerebral artery (ACA) at a depth of 55 to 70 mm, posterior cerebral artery (PCA) at a depth of 55 to 70 mm, posterior cerebral artery (PCA) at a depth of 55 to 70 mm, VAs at a depth of 55 to 70 mm, and basilar artery (BA) at a depth of 70 to 110 mm. Vessel identification was based on published criteria.12 The transtemporal and transforaminal approaches were used during routine examinations. Two methods were combined for this examination. We initially used transcranial color-
coded duplex sonography (TCCD) in the power-mode-based mode, which was performed with the HDI 3000 device (ATL). The probe had the phased-array characteristic with a frequency between 2 and 3 MHz. The sample volume was 7.5 mm. In case of an inconclusive test result, transcranial Doppler (TCD) was additionally applied (Multi-Dop P, DWL) with a 2-MHz transducer. Sample volume was 10 mm, and depth was changed in 2-mm steps.

Third, TU examination was subsequently classified as diagnostic, ie, full confidence in the quality of the ultrasound result, or nondiagnostic, ie, insufficient quality of the examination results. In the latter case, the examination was repeated by a second experienced ultrasonographer (H.W. or P.Z). Failure of the second examiner to obtain a diagnostic result resulted in subsequent examination under application of UCA.

Fourth, the galactose-based UCA was applied in a concentration of 300 mg/mL at a velocity of 1 mL/min through an injector (Medrad Pulsar). Before injection, alternative diagnostic methods were offered to the patients, and the aim and characteristics of the planned examination were discussed in detail. Informed consent was obtained from all patients in whom UCA was applied. After injection of the UCA, TU was selectively repeated for vessels in which the initial examination was not classified as diagnostic. Examination was done by the same examiners, with 1 examiner performing the examination and the other observing the results on the display of the ultrasonic device. At the end, both assessed the result as diagnostic, ie, all the diagnostic questions were answered; improved, ie, the visibility of the vascular architecture was improved but diagnostic questions remained (eg, stenosis could not be excluded for part of the vessel); or not improved.

### Part 2
During a 3-month time period, the results of all ultrasonic examinations performed with UCA-enhanced TU were compared with 3-dimensional time of flight (3D-TOF) MR angiography (MRA). This was performed with a 1.5-T whole-body scanner (Magnetom Vision, Siemens) using a circular, polarized head coil and the following settings: repetition time, 35 ms; echo time, 7.2 ms; flip angle, 20°; matrix, 200×512; field of view, 150×200 mm; slab thickness, 36 mm; partitions, 24; effective slice thickness 1.5 mm; acquisition time, 6:44 minutes). Evaluation of the MRA findings was performed by an experienced radiologist (J.B.) who was blinded to the results of TU. A ≥50% diameter reduction was classified as stenosis. This was assessed by evaluation of the maximum intensity projections and the primary slices.

Ultrasound criterion for intracranial stenosis was a segmental flow acceleration that could become obvious by an acceleration of >50% from baseline, a side difference >30 cm/s (V-mean) between corresponding intracranial arteries, or absolute V-mean values >80 cm/s for the MCA and ICA, >75 cm/s for the ACA, >60 cm/s for the PCA and VA, and >65 cm/s for the BA. A spectral broadening with low-frequency parts in the spectra and harmonic vibrations of the vessel wall (muscular murmurs) were noted and served as secondary criteria, interpreted only as vessel stenosis if they were associated with a segmental flow acceleration.13

### Results

#### Part 1
TU results of 687 patients were evaluated during the study period. All patients were white. The mean ± SD age was 64 ± 9 years (61% male, 39% female). Indication for application of ACU was found in 61 patients (8.8%). One patient with severe heart failure and 1 women with Raynaud’s syndrome were excluded for safety reasons, and 2 additional patients refused consent. Thus, 57 patients (8.3%) were examined with UCA-enhanced TU. Their mean age was 67 ± 7 years, and female sex was predominant (n = 29, 51%). UCA-enhanced TU was necessary for transtemporal insonation in 38, transfemoral in 18, and both approaches in 1.

### Pathological Findings After Application of the UCA Levovist in 57 Patients Over a Time Period of 6 Months

<table>
<thead>
<tr>
<th>Pathological Findings on TU</th>
<th>Detectable Only After Application of Levovist, n</th>
</tr>
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<tbody>
<tr>
<td>Transtemporal (n = 115 arteries)</td>
<td></td>
</tr>
<tr>
<td>ICA/MCA stenosis/occlusion</td>
<td>17</td>
</tr>
<tr>
<td>ACA stenosis</td>
<td>2</td>
</tr>
<tr>
<td>PCA stenosis</td>
<td>4</td>
</tr>
<tr>
<td>Collateralization</td>
<td></td>
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<tr>
<td>A Com Ant</td>
<td>1</td>
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<tr>
<td>A Com Post</td>
<td>1</td>
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<tr>
<td>Transfemoral (n = 31 arteries)</td>
<td></td>
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<tr>
<td>BA stenosis/occlusion</td>
<td>5</td>
</tr>
<tr>
<td>VA stenosis</td>
<td>2</td>
</tr>
</tbody>
</table>

A Com Ant indicates anterior communicating artery; A Com Post, posterior communicating artery.

A total of 112 arteries could be successfully assessed in 38 patients with UCA-enhanced TU. The signal improvement led to a diagnostic result in 86 arteries. In 26 arteries, the Doppler signal improved but was still insufficient. No signal improvement was observed in 1 patient (3 arteries). Thus, contrast enhancement led to a diagnostic result in 75% of the arteries examined via the transtemporal approach. Signal quality improved in 31 arteries (18 patients) during transfemoral TU. UCA-enhanced TU led to a diagnostic result in 25 arteries and to an improved result in 6 arteries. Thus, a diagnostic result was achieved in 81% of the examined VAs and BAs using UCA-enhanced TU. The diagnostic benefit after application of the UCA is summarized in the Table. Pathological findings potentially influencing diagnostic and therapeutic decisions were obtained in 30 of 146 arteries (21%), whereas UCA-enhanced TU resulted in diagnostic evaluation of collateral pathways in 2 cases.

#### Part 2
During the 3-month study period, 312 patients were examined with TU. The indication for use of UCA was met in 29 patients (9.3%), none of whom rejected its application. All patients were subsequently examined with 3D-TOF MRA. An intracranial stenosis was found in 18 cases on UCA-enhanced TU (ICA or MCA, n = 13; ACA, n = 1; PCA, n = 1; BA, n = 2; VA, n = 1). In 15 cases (83%), this diagnosis was confirmed by MRA. In 2 cases (1 ICA stenosis and 1 VA stenosis), MRA revealed a stenosis of <50%. Finally, in 1 case with BA stenosis diagnosed by UCA-enhanced TU, MRA merely showed an elongation. UCA-enhanced TU disclosed normal findings in the remaining 11 cases. This was confirmed by MRA in 9 cases (82%), whereas MRA revealed pathological findings in the remaining 2 cases (mild [60%] ACA stenosis in 1 case and a very short stenosis of the right VA at the transition to the BA in the other). Spectral broadening without flow acceleration was observed on UCA-enhanced TU in the latter case. Because the patient had a history of recurrent brainstem symptoms, he underwent intra-arterial digital subtraction angiography (DSA). This
revealed a very short, high-grade stenosis of the VA, which led to oral anticoagulation.

The sensitivity and specificity of UCA-enhanced TU were thus high (83% and 82%, respectively). In 3 of the 29 patients, discrepancies between the 2 methods were caused by grading of the stenoses in MRI and TU. In a further case, an elongation mimicked a stenosis in TU, whereas no explanation could be found for the final case, despite repeated examination with TU.

**Discussion**

This is the largest prospective study on the frequency of use of UCA in TU and its diagnostic benefit in a routine clinical setting. The intracranial vessels could not be reliably evaluated in 8.8% of the patients with standard TCD and TCCD. UCA application improved diagnostic evaluation of the vessels to 75% during transtemporal and 81% during transforaminal insonation. Discrepant results of UCA-enhanced TU and MRA imaging were observed in 17% of the patients tested.

The percentage of patients requiring UCA enhancement in the present study is markedly lower compared with a previous report that analyzed the number of acute stroke patients in whom UCA was necessary for TCCD examination (8.8% versus 20%, respectively). Several reasons may have contributed to this discrepancy. First, Doppler signals are still visible in TCD when TCCD fails to detect them. Second, we used power-based TCCD that might have advantages compared with the frequency-based TCCD. Third, examination of the patients by 2 examiners increases the chances of finding an optimal bone window. Our findings suggest that the combined use of both ultrasound modalities could potentially decrease the indications for UCA application.

The application of UCA increased the diagnostic information in 75% of patients examined in our study during transtemporal insonation. This is in line with previous studies that analyzed the benefit of UCA application during transtemporal insonation with TCCD. An improvement in the signal quality for the posterior circulation after application of UCA was also reported, although the BA could be visualized only over a mean distance of 1.7 cm. We were able to visualize the complete posterior circulation, including the distal part of the BA, in 81% of patients in our study, probably because both TCD and TCCD were used. Application of UCA increased the diagnostic information of TU in our unselected patient group and resulted in the identification of a stenosis of the basal cerebral arteries in 21% of cases and evaluation of collateral pathways in another 2 of 57 examined cases (3.5%). These results indicate a significant diagnostic benefit after the application of UCA. The high rate of pathological findings in the present study is probably due to patient selection of a tertiary referral center.

We are able to document that UCA-enhanced TU possesses a high specificity and sensitivity compared with 3D-TOF MRA. This may indicate that the impact of UCA on intracranial flow velocities and the signal quality by “bubble noise” may be overestimated in clinical practice. We achieved an agreement for both diagnostic modalities in 83% of cases (24 of 29). Although discrepant findings between TU and MRA were found in 5 cases (17%), these involved only the degree of stenosis in 3 cases and were caused by vessel elongation in 1 case. UCA-enhanced TU thus led to a definitively false-negative result in only 1 case with a short stenosis of the right VA. The examiners noted a disturbed flow pattern but observed no corresponding flow acceleration. This was most probably due to the fact that the applied sample volumes of 10 and 7.5 mm (TCD and TCCD, respectively) were too high to record the high-frequency parts of the spectra. After reduction of the sample volume to 3 mm, we were able to record a segmental flow acceleration. Failure to diagnose a stenosis because of the use of a high sample volume appears to be a pitfall of this technique.

Obviously, the validity of our findings would be higher had we used intra-arterial DSA instead of 3D-TOF MRA as the gold standard. However, 3D-TOF MRA has a high sensitivity and specificity (>85%) compared with DSA. Additionally, DSA is an invasive procedure, which would hardly be justified in most patients enrolled in this study.

In conclusion, application of UCA was necessary in 8.8% of patients. The yield of UCA-enhanced TU in these selected patients was high; the same was true for its sensitivity and specificity for the diagnosis of intracranial stenosis compared with 3D-TOF MRA.

**References**


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